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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,645	11/13/2001	Menzo Jans Emco Havenga	5006.1US	4875

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EXAMINER
MARVICH, MARIA

ART UNIT	PAPER NUMBER
1636	//

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,645	HAVENGA ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *24-27,29-37 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,28 and 38-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This office action is in response to an amendment and response to restriction requirement filed 5/27/03 as paper No. 9. Claims 1-47 are pending in this application.

Election/Restrictions

Applicant's election without traverse of Group I in Paper No. 9 is acknowledged.

Group VII Claim 27, drawn to a method for generating a nucleic acid library classified in class 536, subclass 23.1.

Group VIII. Claim 31, drawn to a method of tissue engineering classified in class 435, subclass 455.

Group IX Claim 47, drawn to a method of generating a packaging cell line, classified in class 435, subclass 377.

Newly amended claims 27, 31 and 47 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The nucleic acids of group I and the methods of group VIII and IX are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP 806.05 (h)). In the instant case, the methods can be practiced with nucleic acids other than the nucleic acids of group I, a nucleic acid delivery vehicle with tissue tropism for mesenchymal stem cells provided by at least a part of a virus capsid. For example, a gene of

interest, which is not linked to a viral capsid protein can be microinjected or transfected into primary cells. The products of Group I are unrelated to the method of Group VII.

Although there are no provisions under the section for "Relationship of Inventions" in MPEP 806.05 for inventive groups that are directed to different methods, restriction is deemed to be proper for the following reasons: The methods of Groups I and Groups VII (claim 27), Group VIII (claim 31) and Group IX (claim 47) utilize distinct and separate method steps and have distinct outcomes. The methods of Group I and VII do not utilize any of the same steps and the outcome of group I is production of a nucleic acid delivery vehicle and delivery of the nucleic acid delivery vehicle to mesenchymal stem cells while the outcome of group VII is generation of a nucleic acid library. Group I is related to the method steps of Group VII and Group IX as all involve introduction of a nucleic acid delivery vehicles but the methods differ in that the method of Group VIII is directed towards tissue engineering that further requires that a nucleic acid (gene) be expressed and Group I does not involve this step. The method of Group IX involves transforming the host cell with nucleic acids encoding replication proteins so that the cell can support replication of the nucleic acid delivery vehicle. The outcome of Group VIII is a tissue altered due to the expression of a nucleic acid of interest and of Group IX is the production of a packaging cell while the outcome of Group I is the introduction of a nucleic acid into mesenchymal cells.

These inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, Group I (435/320.1) versus Group VII (536/23.1) versus Group VIII (435/455) versus Group IX (435/377). Therefore, since claims 1-

23, 28 and 38-46 have been elected in Paper No. 9, claims 24-27, 29-37 and 47 have been withdrawn from consideration as being directed to a non-elected invention.

Summary of Invention

The instant invention recites a nucleic acid delivery vehicle having at least a tissue tropism for mesenchymal stem cells and having at least partially reduced tissue tropism for liver cells. A single working example of such a delivery vehicle in the specification is a chimeric adenovirus consisting of the adenovirus 5 genome deleted of the ad5 fiber region, which is replaced with the fiber from ad16 (subgroup B).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-23 and 38-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Crystal et al. US 6,127,525.

Crystal et al teach recombinant adenovirus in which the fiber protein is replaced in its entirety or in part with sequences of a fiber protein from a different serotype of adenovirus

(column 11, line 55-58). Specifically disclosed serotype and adenovirus of the invention are serotype C (Ad5) replaced with fibers from serotype B (Ad16) (column 4, line 32-41). Therefore, the recombinant adenovirus of Crystal et al comprises ad5 vectors with the entire fibers from Ad16 (ad5fib16). The adenovirus is replication deficient and includes deletion in the E1 gene (column 15, line 9-34). The recombinant adenovirus can function as a transfer vector and is used to deliver a passenger gene to a target cell or host (column 16,line 18-23) and has a decreased ability to be recognized by an antibody (host immune response) (column 4, 42-45). While the chimeric vector of Crystal et al is used for the avoidance of neutralizing antibodies, this does not exclude its use in altered tropism toward mesenchymal cells as it has tropism for mesenchymal cells and reduced tropism for liver cells inherent in its structure. This inherency is taught by applicant's experimental evidence with an ad5fib16 chimera, which were more efficient at transducing mesenchymal cells with GFP or LacZ marker genes than Ad5 (page 28, [0080]. In Crystal et al., processes for the generation of delivery vehicles comprised of fibers of ad16 in an ad5 backbone are taught. These processes are exemplified by but not limited to a chimeric ad5fib7 construct. Crystal et al teach that the method can be used to construct vectors with other fiber modifications (column 17, line 63- column 18, line 7). In this process 293 cells are infected with the chimeric adenovirus and the resultant virus with a substituted fiber is produced.

Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional

characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 1-13, 18-19, 21, 38-41 are rejected under 35 U.S.C. 102(a) as being anticipated by JP02000157289A.

The invention of JP02000157289A discloses a gene delivery medium obtained by combining nucleic acid encoding a fiber protein composed of at least one tissue tropism-determining fragment of a fiber from ad15 with a non-fiber capsid protein fragment from ad5 to generate a recombinant adenovirus capsid. While the recombinant capsid has tropism form smooth muscle cells, this does not exclude its use in altered tropism toward mesenchymal cells as it has tropism for mesenchymal cells and reduced tropism for liver cells inherent in its structure. This inherency is taught by applicant's experimental evidence with an ad5fib16 chimera, which were more efficient at transducing mesenchymal cells with GFP or LacZ marker genes than Ad5 (page 28, [0080].

Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23, 28 and 38-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear for reciting a "vehicle having at least a tissue tropism". It is unclear whether the vector is intended to have tropism for at least mesenchymal cells or to have functions other than tropism.

Claim 2 is unclear for reciting "reduced tropism for liver cells". It is unclear how the tropism for liver cells is reduced. Neither the specification nor the prior art provide a method of measure of reduced tropism. The metes and bounds of the claim are unclear.

Claims 3-23, 28 and 38-46 are vague for reciting a capsid or a functional derivative and/or analogue thereof and alternatively a capsid (or fiber) or functional parts, derivatives and/or analogues. It is unclear the nature and number of steps required to obtain a "derivative" of a protein from a viral capsid. The metes and bounds of the claimed subject matter are unclear.

In so far as the above recited claims recite functional parts or functional derivatives. It is unclear what function refers, the specific tropism function or all functions mediated by a virus capsid or fiber? The metes and bounds of "functional" are also unclear.

Claim 7 is vague for reciting, "a fiber protein derived from a subgroup B adenovirus a functional derivative and/or analogue thereof". It is unclear whether the functional derivative and/or analogue thereof describe the protein or adenovirus.

Claims 9, 21, 40, 41 and 45 are vague for reciting a capsid derived from adenovirus. It is unclear the nature and number of steps required to obtain a "derivative" of a protein from a viral capsid. The metes and bounds of the claimed subject matter are unclear.

Claim 9 is unclear for reciting a protein derived from an adenovirus not belonging to subgroup B, or a functional part, derivative and/or analogue thereof. It is unclear whether functional part, derivative and/or analogue refers to the adenovirus or the protein.

Claim 20 is unclear for reciting that the nucleic acid has been deprived of the capacity to express. It is not clear what is depriving the nucleic acid of the ability to express or how the nucleic acid is deprived.

Claim 22 and 23 are rejected for reciting providing a cell with the "means for the production of an adenovirus". It is unclear if this is a part of applicants' invention (which must be made *de novo*) or the step of providing the means merely involves obtaining prior art components necessary to generate an adenovirus fiber protein.

Claim 46 is unclear for reciting a cell that is or is derived from a PER.C6 cell. It is unclear how closely related the derived cells are to the original PER.C6 cell and it is unclear what procedures were used to derive the cells. The metes and bounds of the claimed subject matter are unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-23, 28 and 38-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim a genus of nucleic acid delivery vehicles having tissue tropism for mesenchymal stem cells and at least partially reduced tissue tropism for liver cells.

Applicants claim a genus of virus capsids and proteins or functional derivatives and/or analogues thereof with tissue tropism for mesenchymal stem cells and at least partially reduced tissue tropism for liver cells.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus. Applicants claim a genus of nucleic acid delivery vehicles that can be of any type of delivery vehicle of which the only disclosed vehicle is an adenoviral vector. There is no actual reduction to practice or clear depiction of what structures or properties are required for generation of any delivery vehicle with tissue tropism for mesenchymal stem cells. The specification teaches only the generation of a chimeric adenovirus comprised of adenovirus of subgroup 5 (ad5) comprised of fiber from 16 (ad5fib16) with greater infectivity of mesenchymal cells than that of wild-type ad5. Neither

applicant not the prior art provide a correlation between the structure of any nucleic acid delivery vehicle and their tropism. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus. Given the diversity of claimed nucleic acid delivery vehicles and the lack of written disclosure of the structural characteristics of these vehicles, the lack of written disclosure of the functional characteristics that provide for tropism for mesenchymal cells beside ad16 fiber, it is concluded that applicant was not in possession of their invention.

The invention claims as an essential element that the derivatives have tissue tropism for mesenchymal stem cells and at least partially reduced tissue tropism for liver cells. It is demonstrated that chimeric adenovirus comprised of AD5 adenovirus encoding fiber from 16 (ad5fib16) infect Mesenchymal cells better than ad5 as measured by amount of GFP, marker gene, expression in MSC (example IV). However, there is no actual reduction to practice or clear depiction of what structures or properties are required for generation of a delivery vehicle with tissue tropism for mesenchymal stem cells and at least partially reduced tissue tropism for liver cells. Neither applicant not the prior art provide a correlation between the structure of the recited and their tropism. Nor are the methods for determining whether tropism is "reduced" provided in the specification. Given the diversity of derivatives and the inability to determine which derivatives will also have the essential element of specific tropism and "reduced" tropism, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 43 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for modifications in nucleic acids that reduce the capacity of the immune system to mount an immune response, does not reasonably provide enablement for modifications in nucleic acids that disable the capacity of the immune system to mount an immune response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) State of the art. The invention recites a nucleic acid delivery vehicle with modified nucleic acid, which is modified such that an immune response is disabled in a host system.

While much effort has been directed at generating adenoviral vectors that can evade the immune system, success to date has been very limited. It is known that adenoviral activate innate immune response in host systems which is caused by the viral capsid (Liu and Muruve,

Gene Therapy (2003) page 935, column 2. last paragraph). While advances have been made in reducing the immune response, the response has been disabled. Reduction of the response has been attempted by alteration of adenoviral nucleotides (Crystal et al. US 6,127,525 column 18, line 49-56) but more recently by inhibition of endosomal escape of the adenovirus (page 937, column 2, paragraph 2).

2) Unpredictability of the art. It is highly unpredictable that any modifications of the adenoviral nucleic acid would result in a adenoviral vector such that the immune response is disabled. The capsid proteins that are required for entry into the host cell elicit the host response. To date, no work has shown that this response can be disabled.

3) Number of working examples. Applicants disclose no working examples for how to modify the nucleic acid such that the immune response is disabled.

4) Amount of guidance provided by applicants. No guidance is provided for alterations that would need to be made in the nucleic acid of the adenovirus such that an immune response by a host system is disabled.

5) Nature of invention. This invention requires a combination of molecular cloning, viral and cell culture techniques.

6) Level of skill in the art. The level of skill in the art covering this invention was high at the time of invention; however, given the unpredictability of the art, the poorly developed state of the art, the lack of working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue experimentation to practice the claimed invention.

7) Scope of the invention. This invention has a broad scope in that it recites a recombinant adenoviral vector with altered tropism to a mesenchymal cell.

In view of predictability of the art to which the invention pertains and the lack of established clinical protocols to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification for how to reasonably determine how to modify the nucleic acid of the recombinant chimeric adenoviral vector such that the immune response is disabled.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue experimentation and excessive experimentation in order to practice the claimed invention

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3291.

Maria B Marvich, PhD
Examiner
Art Unit 1636

June 30, 2003

Gerald D. Jeffers Jr.
PATENT EXAMINER